Remarks

The Specification has been amended to correct various typographical errors in the Application as filed. Applicant submits that no new matter has been added to the Specification by these changes.

Claims 1-281 are pending in the Application, and claims 1-49, 56-59, 61-62, 67-78, 82-83, 92-93, 98-101, 105-107, 110, 113-114, 117-121, 124, 127-128, 130-135, 140-141, 151-152, 157-159, 176-183, 186-187, and 192-281 have been withdrawn from further consideration by the Examiner, 37 CFR §1.142(b), as being drawn to non-elected inventions. Claims 50-55, 60, 63-66, 79-81, 84-91, 94-97, 102-104, 108-109, 111-112, 115-116, 122-123, 125-126, 129, 136-139, 142-150, 153-156, 160-175, 184-185, and 188-191 stand rejected. Claims 50, 89, 108, 116, and 161 are amended as above. No new claims are added. No new matter is added to the Specification by these changes. Applicant respectfully requests reexamination and reconsideration of the case, as amended. Each of the rejections levied in the Office Action is addressed individually below.

I. **Rejection under 35 U.S.C. §112, second paragraph, as being indefinite**. Claims 50, 60, 63-66, 79-81, 84-91, 94-97, 102-104, 109, 111-112, 115-116, 122-126, 129, 136-139, 142-150, 153-156, 160-175, 184-185, and 188-191 stand rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 50, 60, 63-66, 78-81, 84-91, 94-97, 102-104, 108-109, 111-112, 115-116, 122-126, 129, 136-139, 142-150, 153-156, 160-175, 184-185, and 188-191 were rejected under 35 USC §112, second paragraph, as being incomplete for omitting essential steps. Specifically, the Examiner maintains that the omitted step is administering the pAPC to a subject so as to modulate an immune response. Applicant disagrees that the method of modulating an immune response requires the administration of the cells to a subject, but nonetheless, in order to further the prosecution of the present Application, Applicant has amended the preamble of claim 1 to

recite a method of modulating presentation of an antigen and requests that the rejection be removed since there is no omission of an essential step in these amended claims.

Independent claims 109 and 160 recite contacting the pAPC displaying the antigen with T cells under specific conditions to elicit the desired T-cell response. Applicant submits that modulating the response of T cells upon exposure to the pAPC constitutes modulating an immune system response to an antigen, and therefore, no essential step has been omitted. Applicant requests that the rejection be removed.

Claim 89 has been rejected under 35 USC §112, as having no antecedent basis for the term "administering". Claim 89 has been amended to recite the step exposing rather than administering and therefore to obviate this rejection.

Claim 161 has been rejected under 35 USC §112, as having no antecedent basis for the term "mature pAPC". Claim 161 has been amended in order to obviate the rejection by removing the adjective mature.

Claim 116 has been amended to correct the typographical error present in the claim. Applicant would like to thank the Examiner for pointing out this error in the claim.

Claim 108 has been amended so as not to depend from non-elected claim 101, and therefore, it is made proper.

II. <u>Rejection under 35 U.S.C. §103, as being unpatentable over U.S. Patent 5,994,126 in view of WO98/37919 and Romagnani (1997)</u>. Claims 50-55, 60, 64-66, 97, 102-104, 108-109, 111-112, 115-116, 122-126, 129, 147, 156, 160-167, 175 and 191 stand rejected under 35 USC §103 as being unpatentable over U.S. Patent 5,994,126 in view of WO98/37919 and Romagnani ("The Th1/Th2 paradigm" *Immunology Today* 18(6):263-266, June 1997). Examiner states that the '126 patent teaches a method of modulating an immune system response to an antigen comprising the steps of isolating professional antigen presenting cells (pAPC) and exposing them to antigen. Examiner admits that the '126 patent does not teach "the modulation of the immune response away from a Th2 response", and therefore it cannot by itself anticipate or render obvious the elected species of the claimed invention. Examiner relies on WO98/37919 to teach that an immune response can be redirected away from a Th2 response using CpG dinucleotides. The reference by Romagnani teaches that certain diseases and conditions are mediated by a Th1

response while others are mediated by a Th2 response. Examiner maintains that the elected claimed invention of the present Application would have been *prima facie* obvious to one of ordinary skill in the art given the combined teachings of these three references.

Applicant, however, disagrees with the Examiner's conclusion concerning the elected species of the claims being examined. First of all, there is no motivation to combine the teachings of the '126 patent with those of WO98/37919 in such a way as to render the claimed invention obvious. The teachings of WO98/37919 are limited to the administration of CpGs to natural (NK) cells (see page 4, lines 19-20); the '126 patent teaches isolation of pAPC. Nowhere in WO98/37919 is administration of CpG to pAPC discussed; nowhere in the '126 patent is it suggested that isolated pAPC should be treated like NK cells. Absent the teachings of the present Specification, one of ordinary skill in this art would not combine these references to render obvious the claimed invention. In particular, one of ordinary skill in this art would not look to WO98/37919 to find agents to be administered to pAPC in order to modulate the presentation of an antigen.

Furthermore, WO98/37919 teaches the use of nucleic acids containing at least one unmethylated cytosine-guanine (CpG) dinucleotide in treating pulmonary disease and pulmonary diseases with an immunologic component. The reference does not suggest that exposing isolated cells of the immune system (*e.g.*, dendritic cells, antigen presenting cells) to CpG dinucleotides would produce the same modulation of the immune system response, nor does it suggest treating any diseases other than pulmonary disorders. In particular, the reference does not suggest using pAPCs to affect the immune system response. The third reference by Romagnani is merely a general review of Th1 versus Th2 responses and could not possibly provide the teachings or suggestions that would be required for the cited references to render obvious the claimed invention. In view of the elected species being examined, without a suggestion to combine these references, the Applicant submits that the combination of these references does not render the claimed invention obvious.

Even if there were a suggestion or motivation to combine these three references, there would be no reasonable expectation of success of achieving the claimed invention. WO98/37919 only teaches the activation of natural killer cells by CpG dinucleotides and does not mention any affect of CpG dinucleotides on professional antigen presenting cells. Professional APC would

not be expected *a priori* to behave in the same way as NK cells. Also, exposing isolated cells to CpG and then administering those cells to the subject would be found by one of ordinary skill in the art to be unlikely to deliver the desired modulation of the immune response that was seen upon administration of CpG to the whole body subject. The third reference by Romagnani, merely being a general review of Th1 versus Th2 immune responses, also could not possibly suggest a reasonable expectation of success. Without a reasonable expectation of success, the references, even if there existed a suggestion to combine them, do not render the claimed invention obvious. Applicant respectfully submits that the rejection therefore be removed due to the lack of suggestion to combine the two references and the lack of reasonable chance of success.

Applicant also wishes to point out that the foregoing arguments have been made in view of the election of group and species made in the Response to the Restriction Requirement mailed April 3, 2000, wherein the elected invention comprises a method of modulating an immune system response away from a Th2 response, said elected species consisting of pAPC being dendritic cells, the factor being CpGs, the antigen being a crude antigen preparation, the targeting agent being an Fc receptor ligand, and the encapsulating device being a liposome. Applicant submits that the scope of claim 50 as conceived by the Inventors and as written in the Specification covers a method of modulating an immune system response in general without the limitation, away from a Th2 response. Applicant reserves the right to pursue the intended broader scope of claim 50 later.

III. <u>Rejection under 35 U.S.C. §103, as being unpatentable over U.S. Patent 5,994,126, WO98/37919, and Romagnani in view of Maurer *et al*</u>. Claims 63, 79-81, 84-86, 136-139, 142-144, 168-169, 184-185, and 188-190 stand rejected under §103 as being unpatentable over U.S. Patent No. 5,994,126 in view of WO98/37919 and Romagnani (1997), as applied to claims 50-55, 60, 64-66, 97, 102-104, 108-109, 111-112, 115-116, 122-126, 129, 147, 156, 160-167, 175, and 191, and further in view of Maurer *et al.* (*Dendritic Cells in Fundamental and Clinical Immunology*, 1997). The '126 patent, WO98/37919, and reference by Romagnani have been discussed *supra*. The Examiner maintains that Maurer *et al.* teach that an Fc receptor ligand can facilitate the uptake of antigen by a dendritic cell and that one of ordinary skill in the art at the

time the invention was made would have been motivated to combine an Fc receptor ligand "targeting agent" with the antigen to facilitate the uptake of said antigen by the isolated dendritic cells.

Applicant maintains that since there is no suggestion or motivation to combine the first three references and additionally there would be no reasonable expectation of success, the teaching of Maurer *et al.* do not render the claimed invention obvious. The first three references have been discussed *supra*. Without a teaching of modulating the immune response by isolating APCs and exposing them to agents such as CpG in order to direct the immune response away from a Th2 response, the rejected claims are not rendered obvious even though Maurer *et al.* disclose a targeting agent associated with an antigen. The Applicant requests therefore that the rejection be removed.

IV. Rejection under 35 U.S.C. §103, as being unpatentable over U.S. Patent 5,994,126, WO98/37919, and Romagnani in view of WO98/33520. Claims 87-89, 145-146, 148, and 170-173 stand rejected under 35 U.S.C. §103 as being unpatentable over U.S. Patent 5,994,126 in view of WO98/37919, Romagnani (1997), as applied to claims 50-55, 60, 64-66, 97, 102-104, 108-109, 111-112, 115-116, 122-126, 129, 147, 156, 160-167, 175, and 191, and further in view of WO98/33520. Examiner maintains that WO98/33520 teaches the use of liposomes as encapsulating devices for antigens to increase their potency and clinical effectiveness. Although this reference may teach the use of a carrier to deliver antigen and immunomodulators to antigen presenting cells, there still needs to be a teaching that the delivery of agents such as CpG along with antigen to APCs can lead with reasonable success to the modulation of the immune response away from a Th2 response. Without such a teaching, the rejected claims are not rendered obvious, and the Applicant requests that the rejection be removed.

V. Rejection under 35 U.S.C. §103, as being unpatentable over U.S. Patent 5,994,126, WO98/37919, Romagnani, and WO98/33520 in view of Maurer *et al*. Claims 90-91, 94-96, 149-150, 153-155, 174, 184-185, and 189-190 stand rejected under 35 USC §103, as being unpatentable over U.S. Patent 5,994,126 in view of WO98/37919, Romagnani (1997), and WO98/33520, as applied to claims 50-55, 60, 64-66, 87-89, 97, 102-104, 108-109, 111-112, 115-

116, 122-126, 129, 145-148, 156, 160-167, 170-173, 175, and 191, and further in view of Maurer *et al.* (1997). In light of the forgoing arguments related to the cited references, the Applicant respectfully submits that the rejected claims are not rendered obvious and requests that the rejection be removed.

In view of the forgoing arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner For Patents, Washington, D.C. 20231
on 9/21/00
Susan M. Blenkhorn

Appendix A

50. (Amended) A method of modulating presentation of an antigen, the method comprising steps of:

isolating from an individual one or more pAPC selected from the group consisting of: mature pAPC, immature pAPC, and precursors to pAPC;

exposing the isolated cells to an antigen so that pAPC displaying the antigen are generated, and a pre-determined set of cytokines is expressed.

51. The method of claim 50, further comprising:

administering the antigen-exposed pAPC to a subject whose immune response to the antigen is to be modulated.

52. The method of claim 51, wherein:

the antigen-exposed pAPC are mature pAPC.

53. The method of claim 51, wherein:

the antigen-exposed pAPC are immature pAPC

54. The method of claim 51, wherein:

the pAPC are selected from the group consisting of dendritic cells, B cells, and macrophages.

55. The method of claim 51, wherein:

the pAPC are dendritic cells.

60. The method of claim 50, wherein:

the step of exposing the isolated cells to an antigen comprises exposing the cells to a crude antigen preparation.

63. The method of claim 50, wherein:

the step of exposing the cells to antigen comprises contacting the cells with an antigen that is associated with a targeting agent.

64. The method of claim 50, wherein:

the step of exposing the isolated cells to an antigen further comprises exposing the cells to a composition comprising a factor selected from the group consisting of cytokines and inducing agents, which factor is selected to bias an immune response in a subject away from a Th1 or a Th2 response in a pre-determined manner.

65. The method of claim 64, wherein:

the step of exposing comprises exposing the cells to one or more Th1 inducing agents.

66. The method of claim 65, wherein:

the Th1 inducing agents are selected from the group consisting of LPS, CD40, CD40 ligand, BCGs, oligonucleotides containing CpG motifs, TNF , and microbial extracts.

79. The method of claim 64, wherein:

the one or both of the antigen and factor are associated with a targeting agent.

80. The method of claim 79, wherein:

the association with the targeting agent occurs by means of an interaction selected from the group consisting of covalent bonds, hydrogen bonds, van der Waals interactions, hydrophobic interactions, and combinations thereof.

81. The method of claim 79, wherein:

the targeting agent is selected from the group consisting of mannose receptor ligand and the Fc receptor ligand.

84. The method of claim 79, wherein:

the targeting agent is capable of targeting to intracellular vesicles within pAPCs.

85. The method of claim 79, wherein:

the targeting agent comprises at least the Fc portion of an Ig molecule.

86. The method of claim 79, wherein:

the targeting agent comprises at least the Fc portion of an IgG molecule.

87. The method of claim 50, wherein:

the antigen is encapsulated.

88. The method of claim 64, wherein:

the step of exposing comprises providing the antigen and factor together in an encapsulation device.

89. (Amended) The method of claim 64, wherein:

the step of exposing comprises providing the antigen and the factor in separate encapsulation devices.

90. The method of claim 87, 88, or 89, wherein:

the step of exposing comprises exposing the cells to the encapsulation device in association with a targeting agent.

91. The method of claim 90, wherein:

the targeting agent is selected from the group consisting of mannose receptor ligand and the Fc receptor ligand.

94. The method of claim 90, wherein:

the targeting agent is capable of targeting to particular vesicles within pAPCs.

95. The method of claim 90, wherein:

the targeting agent comprises at least the Fc portion of an Ig molecule.

96. The method of claim 90, wherein:

the targeting agent comprises at least the Fc portion of an IgG molecule.

97. The method of claim 64, wherein:

the step of exposing comprises providing antigen and factor that are associated with one another by means of an interaction selected from the group consisting of: covalent bonds, hydrogen bonds, van der Waals interactions, hydrophobic interactions, and combinations thereof.

102. The method of claim 64, wherein:

the antigen comprises an allergen; and

the factor is selected to bias the immune response to the antigen away from a Th2 response.

103. The method of claim 102, wherein:

the factor comprises a Th1 inducing agent.

104. The method of claim 102, wherein:

the factor is selected from the group consisting of LPS, CD40, CD40 ligand, BCGs, oligonucleotides containing CpG motifs, TNF , and microbial extracts.

108. (Amended) The method of claim 51, further comprising:

administering antigen to the subject.

109. A method of modulating an immune system response to an antigen, the method comprising steps of:

isolating from an individual one or more APC selected from the group consisting of: mature pAPC, immature pAPC, and precursors to pAPC;

exposing the isolated cells to an antigen so that mature pAPC displaying the antigen are generated; and

contacting the antigen-exposed pAPC with T cells so that a pre-determined T-cell response is inhibited.

111. The method of claim 109 wherein:

the pre-determined T cell response is selected from the group consisting of: a Th1 response and a Th2 response.

112. The method of claim 111, wherein:

the Th1 or Th2 response is inhibited through induction of an opposing Th2 or Th1 response.

115. The method of claim 109, wherein:

the step of contacting comprises contacting the antigen-exposed pAPC with T cells in the presence of a Th1 inducing agent, so that the expression of or more Th1 cytokines is induced and a Th2 response is inhibited in the T cells.

116. (Amended) The method of claim 109, wherein:

the step of contacting comprises contacting the antigen-exposed pAPC with T cells in the presence of a Th1 inducing agent selected from the group consisting of LPS, CD40, CD40 ligand, BCGs, oligonucleotides containing CpG motifs, THF , and microbial extracts, so that the expression of one or more Th1 cytokines is induced and a Th2 response is inhibited in the T cells.

122. The method of claim 109, wherein:

the pAPC are selected from the group consisting of dendritic cells, B cells, and macrophages.

123. The method of claim 109, wherein:

the pAPC are dendritic cells.

125. The method of claim 123, wherein:

the step of maturing is performed concurrently with the step of exposing to antigen.

126. The method of claim 109, wherein:

the step of exposing the isolated cells to an antigen comprises exposing the cells to a crude antigen preparation.

129. The method of claim 125, wherein:

the step of exposing further comprises exposing the cells to a factor selected from the group consisting of cytokines and inducing agents.

136. The method of claim 109 wherein:

the antigen is provided in association with a targeting agent.

137. The method of claim 129, wherein:

one or both of the antigen and factor is provided in association with a targeting agent.

138. The method of claim 136 or claim 137, wherein:

the association with the targeting agent occurs by means of an interaction selected from the group consisting of covalent bonds, hydrogen bonds, van der Waals interactions, hydrophobic interactions, and combinations thereof.

139. The method of claim 136 or claim 137, wherein:

the targeting agent is selected from the group consisting of mannose receptor ligand and the Fc receptor ligand.

142. The method of claim 136 or claim 137, wherein:

the targeting agent is capable of targeting to particular vesicles within pAPCs.

143. The method of claim 136 or claim 137, wherein:

the targeting agent comprises at least the Fc portion of an Ig molecule.

144. The method of claim 143, wherein:

the targeting agent comprises at least the Fc portion of an IgG molecule.

145. The method of claim 109, wherein:

the step of exposing comprises providing the antigen in an encapsulation device.

146. The method of claim 129, wherein:

one or both of the antigen and factor is encapsulated.

147. The method of claim 129, wherein:

the antigen and factor are provided together as a single composition.

148. The method of claim 147, wherein:

the antigen and factor are provided encapsulated together in a single encapsulation device.

149. The method of claim 145, 146, or claim 148, wherein:

the encapsulation device is associated with a targeting agent.

150. The method of claim 149, wherein:

the targeting agent is selected from the group consisting of mannose receptor ligand and the Fc receptor ligand.

153. The method of claim 149, wherein:

the targeting agent is capable of targeting to intracellular vesicles within pAPCs.

154. The method of claim 149, wherein:

the targeting agent comprises at least the Fc portion of an Ig molecule.

155. The method of claim 149, wherein:

the targeting agent comprises at least the Fc portion of an IgG molecule.

156. The method of claim 129, wherein:

the step of exposing comprises providing antigen and factor that are associated with one another by means of an interaction selected from the group consisting of: covalent bonds, hydrogen bonds, van der Waals interactions, hydrophobic interactions, and combinations thereof.

160. A method of treating allergy, the method comprising steps of:

identifying an individual who is allergic to an antigen;

providing a composition of pAPC displaying the antigen; and

contacting the composition with T cells of the individual under conditions that inhibit a Th2 response to the antigen.

161. (Amended) The method of claim 160, wherein:

the pAPC are selected for their expression of Th1 cytokines.

162. The method of claim 160, wherein:

the pAPC are selected from the group consisting of dendritic cells, B cells, and macrophages.

163. The method of claim 161, wherein:

the pAPC are dendritic cells.

164. The method of claim 160, wherein:

the step of providing comprises:

isolating from an individual one or more cells selected from the group consisting of mature pAPC, immature pAPC, and precursors to pAPC; and

exposing the isolated cells to the antigen.

165. The method of claim 164, wherein:

the step of exposing the isolated cells to the antigen further comprises exposing the isolated cells to a factor selected from the group consisting of cytokines and inducing agents.

166. The method of claim 165, wherein:

the factor comprises an inducing agent that induces expression of one or more Th1 stimulating cytokines in the pAPC.

167. The method of claim 165 wherein:

the antigen and factor are provided together as part of a single composition.

168. The method of claim 165, wherein:

one or both of the antigen and factor is associated with a targeting agent.

169. The method of claim 164, wherein:

the antigen is associated with a targeting agent.

170. The method of claim 167, wherein:

the antigen and factor are encapsulated together in an encapsulation device.

171. The method of claim 164, wherein

the antigen is encapsulated.

172. The method of claim 165, wherein:

one or both of the antigen and factor is encapsulated.

173. The method of claim 165, wherein:

the antigen and factor are both encapsulated.

174. The method of claim 173, wherein:

the encapsulation device is associated with a targeting agent.

175. The method of claim 164, wherein:

the step of exposing the isolated cells to antigen comprises exposing the cells to a crude

preparation of antigen.

184. The method of any one of claims 168, 169, or 174, wherein:

the association with the targeting agent occurs through an interaction selected from the group consisting of covalent bonds, hydrogen bonds, van der Waals interactions, hydrophobic interactions, and combinations thereof.

185. The method of any one of claims 168, 169, or 174, wherein:

the targeting agent is selected from the group consisting of mannose receptor ligand and the Fc receptor ligand.

188. The method of any one of claims 168, 169, or 174, wherein:

the targeting agent is capable of targeting to intracellular vesicles within pAPCs.

189. The method of any one of claims 168, 169, or 174, wherein:

the targeting agent comprises at least the Fc portion of an Ig molecule.

190. The method of any one of claims 168, 169, or 174, wherein:

the targeting agent comprises at least the Fc portion of an IgG molecule.

191. The method of claim 175, wherein:

the step of exposing comprises providing antigen and factor that are associated with one another by means of an interaction selected from the group consisting of: covalent bonds, hydrogen bonds, van der Waals interactions, hydrophobic interactions, and combinations thereof.